REMARKS

Claims 2, 3 and 6-21 are presently pending. Claims 1, 4, 5 and 22-45 have been canceled without prejudice for being directed to a non-elected invention. Claims 3, 6, 8 and 11-21 have been amended. Claim 3 has been amended to delete non-elected subject matter and claims 6, 8 and 11-21 have been amended to no longer depend from canceled claims. Applicants reserve their right to prosecute the subject matter of any of canceled claims 1, 4, 5 or 22-45, the non-elected subject matter of amended claim 3 or any other unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications. No new matter has been added.

I. The Rejection Under 35 U.S.C. §103

Claims 1-21 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Arance *et al.*, Three-arm Phase II study of temozolomide (TMZ) in metastatic melanoma (MM): preliminary results ("Arance") in further view of Newton, Novel Chemotherapeutic Agents for the Treatment of Brain Cancer ("Newton")[1]. In particular, the Examiner alleges that it would have been obvious to one having ordinary skill in the art to have used the combination of temozolomide and thalidomide for the treatment of brain cancers. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, a reasonable expectation of success is required. *See In re Merck*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986), *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988), MPEP §2143.02. There is nothing in Arance or Newton, either alone or in combination, that provides a reasonable expectation of success in treating cancer by the administration of temozolomide in combination with another cytotoxic agent, let alone treating cancer in combination with thalidomide. In fact, Newton expressly states with respect to temozolomide that "[a]lthough it is active as a single agent, further studies are required to determine it if may be more efficacious in combination with other cytotoxic drugs such as BCNU or cisplatin or with newer agents like marimistat or thalidomide." (*See* page 2824, second sentence of the first

[1] Applicants wish to emphasize that the arguments made herein should not be construed as an admission that either reference, but particularly Newton, is prior art against the pending claims. The instance application claims priority to U.S. provisional application no. 60/250,130, filed December 1, 2000. Thus, an article published thereafter is not prior art.

full paragraph). An indication that further studies are needed certainly does not give one the legally required expectation of success.

Furthermore, one does not find the usually requisite expectation of success in Arance. The clinical results disclosed in Arance suggest that the administration of temozolomide in combination with thalidomide is no more effective for treating metastatic melanoma than treatment with temozolomide alone. *See* Conclusion, last sentence. This result suggests that cancer treatment comprising the administration of temozolmide in combination with thalidomide would not be any more desirable than single-agent therapy and, consequently, would lead one of skill in the art away from combination therapy.

In addition, Applicants submit reference **BM** (Hwu et al., "Phase II Study of Temozolomide Plus Thalidomide for the Treatment of Metastatic Melanoma", *J. Clin. Oncol.* 21:3351-3356 (2003)), authored by the inventor of the present application (Wen-Jen Hwu, M.D.) herewith in a Supplemental Information Disclosure Statement. Dr. Hwu reports in reference **BM** that in a regimen of temozolomide (75 $mg/m^2/d$ x 6 weeks with a 2-week rest between cycles) plus concomitant thalidomide (200 mg/d with dose escalation to 400 mg/d for patients < 70 years old, or 100 mg/d with dose escalation to 250 mg/d for patients ≥70 years old) surprisingly and unexpectedly resulted in twelve patients (32%) having an objective tumor response, with one patient having a complete response and 11 patients having a partial response (*see* reference **BM**, page 3351, Results). In contrast, Arance reports that in regimens of temozolomide alone (200 mg/m^2 every eight hours for five doses), temozolomide (200 $mg/m^2/d$ for days 1-5) and interferon alfa (5 million IU/mL^2 three times a week for four weeks) or temozolomide (150 $mg/m^2/d$ for days 1-5) and thalidomide (100 mg/d for 28 days), only eight (16%) patients had a partial response (with no complete responses indicated) with no difference being indicated between temozolomide treatment alone or with interferon alfa or thalidomide.

Thus, in view of the teachings in the cited references and the surprising and unexpected results set forth in reference **BM**, Applicants respectfully submit that the rejection of claims 2, 3 and 6-21 (claims 1, 4 and 5 having been canceled) under 35 U.S.C. §103 over Arance and Newton cannot stand and must be withdrawn.

II. Conclusion

Applicants respectfully request that the present remarks be made of record in the file history of the present application. An early allowance of the application is earnestly

requested. The Examiner is invited to call the undersigned with any questions concerning the foregoing.

It is believed that no fee is due other than that for the extension of time, however, in the event any other fee is required, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

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Date: October 14, 2003

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